RATIONALIZING HISTORICAL SUCCESSES OF MALARIA CONTROL IN AFRICA IN TERMS OF MOSQUITO RESOURCE AVAILABILTY MANAGEMENT

GERRY F. KILLEEN, AKLILU SEYOUM, AND BART G. J. KNOLS

Ifakara Health Research and Development Centre, Ifakara, Kilombero District, Tanzania; Department of Public Health and Epidemiology, Swiss Tropical Institute, Basel, Switzerland; Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia; Laboratory of Entomology, Wageningen University Research Centre, Wageningen, The Netherlands; Entomology Unit, Food and Agriculture Organization/International Atomic Energy Agency, Agriculture and Biotechnology Laboratory, Seibersdorf, Austria

Abstract. Environmental management of mosquito resources is a promising approach with which to control malaria, but it has seen little application in Africa for more than half a century. Here we present a kinetic model of mosquito foraging for aquatic habitats and vertebrate hosts that allows estimation of malaria transmission intensity by defining the availability of these resources as the rate at which individual mosquitoes encounter and use them. The model captures historically observed responses of malaria transmission to environmental change, highlights important gaps in current understanding of vector ecology, and suggests convenient solutions. Resource availability is an intuitive concept that provides an adaptable framework for models of mosquito population dynamics, gene flow, and pathogen transmission that can be conveniently parameterized with direct field measurements. Furthermore, the model presented predicts that drastic reductions of malaria transmission are possible with environmental management and elucidates an ecologic basis for previous successes of integrated malaria control in Africa before the advent of DDT or chloroquine. Environmental management for malaria control requires specialist skills that are currently lacking in sub-Saharan Africa where they are needed most. Infrastructure and human capacity building in clinical, public health, and environmental disciplines should therefore be prioritized so that growing financial support for tackling malaria can be translated into truly integrated control programs.

INTRODUCTION

Malaria threatens the lives and livelihoods of more than 500 million Africans and exerts such a huge public health burden that it has been incriminated in the continued under-development of the continent as a whole.[1–3] Most of sub-Saharan Africa has stable endemic malaria because climatic conditions ideal for transmission coincide with the ranges of *Anopheles gambiae* Giles, *An. arabiensis* Patton, and *An. funestus* Giles, the most efficient vector mosquitoes in the world.[4,5] In eastern and southern Africa, the proportion of deaths caused by malaria has increased from 18% in the 1980s to 37% in the 1990s.[6] Endemic malaria cripples economies and is estimated to slow economic growth by approximately 1.3% per year.[2] Malaria has been identified as a key contributor to weak economic growth and investment in Africa because it experiences the most intense malaria transmission in the world.[5,7] It is commonplace in tropical Africa for more than half the population to be infected with *Plasmodium falciparum*, by far the most dangerous of the four parasite species that infect humans.[5] Not only does malaria place a huge burden directly upon the health care systems of African nations, it has also been shown that malaria control can have huge macroeconomic impacts and greatly facilitate economic development at national level.[2,8,9] Although some countries in southern Africa are successfully applying integrated malaria control,[10] such programs currently cover only a small proportion of those at risk on the continent.

Since the first transmission models of Ronald Ross, it has been recognized that the epidemiology and control of malaria is inextricably linked to the ecology of its mosquito vectors.[11] Ecologic control of malaria by managing the availability of water and vertebrate host resources[12–18] for mosquitoes is receiving renewed attention, but has seen little application in Africa for more than half a century.[8,19–23] Integrated packages of multiple malaria control interventions, relying heavily on environmental management, proved particularly success-ful in the copper mining regions of Zambia, even before the advent of DDT or chloroquine.[8,21,24] Environmental management has also been successfully applied in African cities, notably Dar es Salaam in Tanzania,[25–30] and may have an important role to play in protecting the rapidly growing urban population of Africa from malaria.[31,32]

The importance of host and larval habitat availability as determinants of malaria transmission intensity and distribution has long been recognized and discussed lucidly in qualitative terms.[12–14] Models of Chagas' disease transmission ecology, as a function of the abundance of various hosts for the triatomine bugs that act as its vector, have yielded valuable insights with practical public health implications.[33] Related behavioral manipulation concepts, such as "push-pull,"[34–37] have proven extremely useful for managing crop pests.[38] However, quantitative studies of such relationships for mosquitoes and malaria transmission remain sparse, resulting in quite limited development of models with which the influence of these ecologic variations can be examined.[39–41] The development of integrated ecologic models will be essential for accurate quantitative evaluation of conventional vector control interventions[42,43] and products of modern genomics technology such as transgenic mosquitoes.[43–45] Here we present a kinetic definition of the term resource availability and use it to elucidate an ecologic basis for the outstanding success of integrated malaria control programs in Africa before the advent of modern domestic insecticides or antiparasitic drugs.[8,21,24]

METHODS

Modeling malaria transmission as a function of resource availability. We define the term *availability* as product of the rate at which individual mosquitoes encounter such a resource (ε) and the likelihood that, once encountered, they will use it (ϕ).[40] This definition is consistent with current under-

standing of insect searching behavior[46,47] and similar but less explicit concepts such as the forage ratio or feeding index.[48,49] As described previously for vertebrate blood meal hosts,[40] the resource-seeking interval (η_r) or length of time spent foraging for a given resource (r) is the reciprocal of the total availability of that resource (A_r). This is in turn the sum of the availabilities of all distinct units (j) of that resource ($a_{r,j}$)

$$\eta_r = 1/A_r = 1/\sum_j^{Nj} a_{r,j} = 1/\sum_j^{Nj} \varepsilon_{r,j}\, \phi_{r,j} \qquad (1)$$

Based on common assumptions,[41,50,51] the length of the gonotrophic period or feeding cycle interval can be considered as the sum of the gestation period (g) and various seeking intervals for the different resources required by the female mosquito (η_r). Sperm and carbohydrate meals are poorly understood resources for female mosquitoes, but are generally considered unlikely to be limiting factors in the field. We therefore only consider time spent searching for vertebrate hosts (η_v) and aquatic habitats (η_a) at the beginning and end of the feeding cycle, respectively, when calculating the length of the gonotrophic cycle

$$f = g + \sum_r^{Nr} \eta_r \approx g + \eta_v + \eta_a \qquad (2)$$

Assuming that all phases of the gonotrophic cycle result in the same daily survival rate (P) for the mosquito, the proportion surviving each feeding cycle (P_f) can be estimated as a function of the total feeding cycle length

$$P_f = P^{g+\eta_v+\eta_o} \qquad (3)$$

The proportion of blood meals taken from humans (Q_h) can be calculated based on their contribution to the total availability of all potential sources of blood. The scenario explored below relates to a vector species for which there are only two important host species, namely humans and cattle.[40] The proportion of blood meals derived from humans can therefore be calculated from the mean availabilities and population sizes of humans and cattle (N_h and N_c, respectively)

$$Q_h = A_h/A \approx N_h\, a_h/(N_h\, a_h + N_c\, a_c) \qquad (4)$$

We assume oviposition input is not limiting to aquatic habitat productivity and that these habitats are saturated at their carrying capacity. Thus the emergence rate of adult vectors (E) is the product of the total availability of those aquatic habitats (A_a) and their mean productivity per encountered habitat (α)

$$E = \alpha A_a \qquad (5)$$

Parameterizing the model. Namawala, a village in the Kilombero floodplain of southern Tanzania, was chosen as the primary center for parameterizing and applying our model because of the detailed quantitative characterization of local malaria transmission and vector biodemography.[52–54] Although this setting is by no means identical to that of the Zambian copper belt half a century ago,[8,21] previous analyses indicate that the impacts of interventions such as insecticide-treated nets on transmission are relatively consistent across endemic settings, regardless of local ecologic variations in the underlying determinants of transmission.[55] Furthermore, Namawala represents a particularly challenging scenario

where transmission is seasonal and intense because of abundant proliferation by *An. arabiensis* during the rice cultivation season.[53,54] As previously reported, we base our estimates of human infectiousness and population size directly upon those reported for this village during the early 1990s.[50] At the time, cattle were absent from Namawala, at least partly because of endemic trypanosomiasis, and negligible feeding on hosts other than humans occurred.[53] For the *An. arabiensis* population in Namawala, the human population of approximately 1,200 results in a mean host-seeking interval of 0.69 days over the course of the main transmission season.[54] Equations 1 and 4 yield estimates for total and mean individual human host availability of 1.45 and 0.0012 successful feeds per night per host seeking vector, respectively. In the absence of any direct estimates, we assume that the abundance of larval habitats during the transmission season in Namawala corresponds to a total availability of three ovipositions per night per aquatic habitat-seeking vector, or a mean habitat-seeking interval of 0.33 nights. This does not mean that mosquitoes lay more than one egg batch, but it merely reflects the rate at which this process occurs on a once-off basis per gonotrophic cycle. We set mean daily survival at 0.90 reflecting an approximate median of estimates for four different holoendemic sites, including Namawala.[50] The number of total (b_h = 2.93) and infectious (β_h = 0.044) human bites per vector lifetime were calculated as described previously,[50] except that the model used nightly rather than entire feeding cycle increments and accounted for superinfection in the estimation of age-specific sporozoite prevalence. These estimates were combined with those reported for the annual human biting rate to calculate emergence rate, E,[50] as 9×10^6 vectors per year, so to approximate this level of mosquito proliferation, we set α, the mean productivity per available habitat, to be 3×10^6 adult mosquitoes per year per encountered aquatic habitat per night (see equation 5). Under these baseline conditions, the model predicts sporozoite prevalence (S) and human biting rate (B_h) levels of 1.5% and 60 bites per person per day, resulting in an entomologic inoculation rate (EIR) of 327 infectious bites per person per year, which compares well with field measurements and represents an improvement relative to previous models.[50,53,54]

Modeling malaria control through resource availability management. Various environmental changes in the form of altered land use, agricultural practice, domestic protection and larval control were then simulated as follows. The effects of draining, filling, and modifying aquatic habitats for immature mosquitoes, as exemplified by environmental modification approaches applied in the Zambian copper belt,[8,21,24] was modeled by reducing aquatic habitat availability in proportion to effective coverage. On the other hand, regular application of oil[8,21] or insecticides[22] to potential breeding sites might not be expected to reduce their availability to ovipositing females, but rather suppress their mean productivity. Thus α was reduced in proportion to coverage with regular larvicide treatment as described for successful programs against this species complex in Brazil and Egypt.[22,56,57] Domestic protection against mosquitoes with physical barriers such as house screening, and untreated bed nets[19,20,58–60] was modeled by assuming an 80% reduction in the feeding likelihood for mosquitoes encountering protected individuals and reducing total human host availability accordingly in proportion to coverage. The abundance of cattle as alternative blood

meal hosts and their proximity to humans have been implicated as important determinants of transmission by east African *An. arabiensis* because, where they are housed separately, they can divert mosquitoes from feeding on humans.[37,40,61,62] If effective tsetse fly control and improved water management were to enable cattle rearing as an alternative agricultural practice, previous analyses have suggested that stocking densities of one animal per person could confer substantial zooprophylactic protection against this particular vector.[40] We therefore consider coverage with such an inadvertent malaria prevention practice as being the quotient of the cattle and human population sizes (N_c/N_h) and simulate the effects of increasing cattle ownership by increasing total cattle (A_c) and overall host availability (A) using previous estimates for the relative availability of cattle.[40] In other parts of Tanzania, cattle have a mean availability to *An. arabiensis* that is approximately 1.6 times that of humans,[40] so we estimate that each head of cattle introduced would increase total host availability by 0.0019 feeds per night per host-seeking vector.

RESULTS

Figure 1 shows the distinctive effects that each of the possible environmental changes outlined would be expected to have on transmission. Larval control, through either regular insecticide application or water management approximated the simple linear effect conventionally associated with targeting immature anophelines.[11,63] Nevertheless, hydrologic environmental modification not only reduced biting rate, but also survival and sporozoite prevalence because of the increased length of time spent foraging for oviposition sites. Environmental intervention to reduce larval habitat abundance was estimated to be slightly more effective than regular larvicide application and the most efficacious of the four simulated environmental interventions, all of which appreciably suppressed transmission. The increased length of time gravid female mosquitoes would spend foraging for a reduced number of suitable oviposition sites was predicted to substantially extend the mean length of the gonotrophic cycle and increase the mortality associated with each feeding cycle. Environmental interventions that targeted adult vectors were predicted to be less effective, but both physical domestic protection and increased cattle density did usefully attenuate transmission intensity by reducing both biting rate and sporozoite prevalence.

Interestingly, zooprophylaxis actually increased vector survival per feeding cycle slightly, but was more effective than domestic screening because of drastically lowered human feeding propensity and parasite acquisition rate. Figure 2 shows that combining zooprophylaxis with physical domestic protection does not result in any strong synergistic interaction. It therefore seems likely that the potential impacts of "push-pull" strategies for malaria control[34–37] can be reasonably predicted using simple multiplication of effects by the individual interventions.[55] Vector dispersal range can also crucially affect the success and evaluation of vector control interventions.[13,42] This model suggests that while zooprophylaxis may curtail dispersal by shortening the host-seeking period of the feeding cycle, both domestic protection and water management approaches may substantially increase dispersal
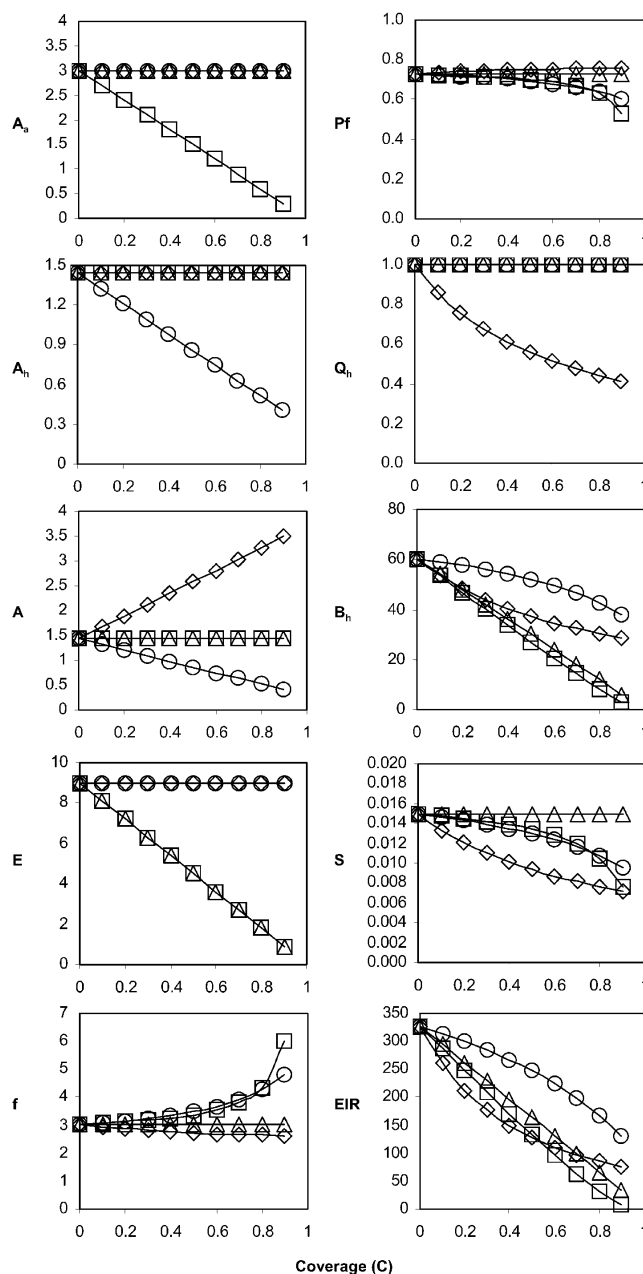

FIGURE 1. Dependence of resource availability, mosquito population dynamics and malaria transmission intensity on environmental management interventions. The plots depict the influence of varying levels of coverage (C) with water management (□), larvicide application (△), physical domestic protection (○), and zooprophylaxis (◇) upon aquatic habitat availability (A_a; ovipositions per aquatic habitat-seeking vector per night), human host availability (A_h = bites per host-seeking vector per night), total host availability (A = bites per host-seeking vector per night), emergence rate (E = millions of vectors per year), feeding cycle length (f = days), proportion surviving per feeding cycle (P_f), human blood index (Q_h), human biting rate (B_h = bites per person per night), sporozoite prevalence (S), and entomologic inoculation rate (EIR = infectious bites per person per year).

by forcing mosquitoes to spend longer in search of human hosts or aquatic habitats, respectively (Figure 1). These relationships are consistent with comparisons between ecologic settings that differ in the abundance of these two key resources.[13,42]
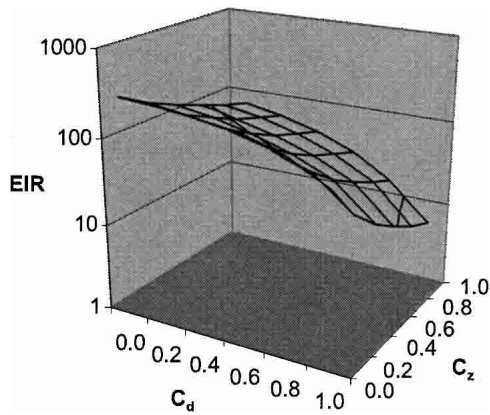
FIGURE 2. Combined effect of varying levels of coverage with domestic physical protection (C_d) and zooprophylaxis (C_z) on annual entomologic inoculation rate (EIR).

An important shortcoming of this model is the assumption that mosquito mortality is uniform throughout the gonotrophic cycle when this is unlikely to be the case is reality.[41,64] If indeed mosquito mortality is considerably higher while searching, increased availability of cattle might increase vector survival further, particularly in scenarios where human population density is low and the searching phase is necessarily long. Thus, the protective effects of reduced human blood feeding might be counteracted more seriously by increased survival, resulting in less dramatic zooprophylaxis or even zoopotentiation.[41] It is striking that the efficacy of such a long-established concept as zooprophylaxis remains controversial for African malaria vector species,[14,40,41,65–67] but our results supports recent studies suggesting that cattle ownership and housing practices can profoundly influence human exposure to malaria in African settings.[37,40,41,61,62,68]

This simulation is consistent with previous models, descriptive analyses, and the proven effectiveness of integrated environmental management for malaria vector mosquitoes.[8,11,21,22,63] The individual and combined effects of the four environmental interventions, at coverage levels that represent ambitious but reasonable targets for implementation, are summarized in Figure 3. While each can significantly re-

duce transmission intensity, combining them in an integrated package could be very effective indeed. Even in this exceedingly challenging setting, predictions indicate that an integrated program including source reduction, modified agricultural practice, and simple housing modifications could reduce transmission intensity from more than 300 to less than 1 infectious bite per person per year. Because total habitat availability is a widely variable parameter in the field, we explored the sensitivity of baseline transmission and expected effects of environmental management to this key determinant. Figure 4 shows how lower aquatic habitat availability, as would be expected in most settings, is expected to result in lower baseline EIR and even greater sensitivity of transmission intensity to hydrologic environmental management.

DISCUSSION

Even quite conservative interpretation of Figures 3 and 4 suggests that drastic reductions of EIR are possible with environmental management in Africa. These simulations parallel the historically observed responsiveness of malaria transmission to environmental change and the proven effectiveness of integrated malaria control initiatives across Europe, Asia, the Americas, and Africa.[8,12,14,20–22] It is particularly notable that many of these spectacular achievements, including those of the Zambian copper belt, were accomplished before the advent of DDT, chloroquine, or any of the similar tools we rely upon so heavily today.

Kinetic models of mosquito resource foraging and utilization behavior, using the explicit definition of availability we have proposed, have considerable potential for exploring the ecology of malaria transmission and control. Here we have used published estimates based on conventional sampling methods for host-seeking female mosquitoes to parameterize these simulations and evaluate the effects of four distinct types of ecologic perturbation on local transmission intensity. Sampling methods for malaria vectors seeking other resources remain grossly underdeveloped[69] and these aspects of their life cycles remain poorly understood.[42,44,45] The understandable focus of medical entomology upon processes directly associated with pathogen transmission[69] has left major
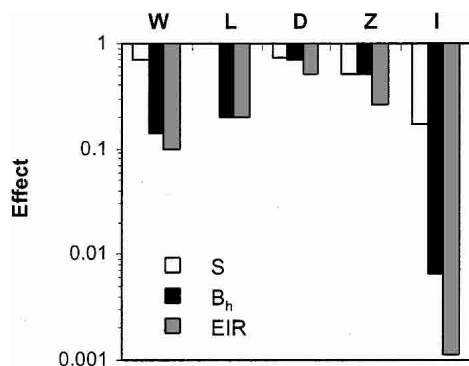

FIGURE 3. Predicted proportional impact of 80% coverage with water management (W), larvicide application (L), physical domestic protection (D), and zooprophylaxis (Z) or an integrated program combining all of these (I) upon sporozoite prevalence (**open bars**), human biting rate (**solid bars**), and entomologic inoculation rate (**gray bars**).
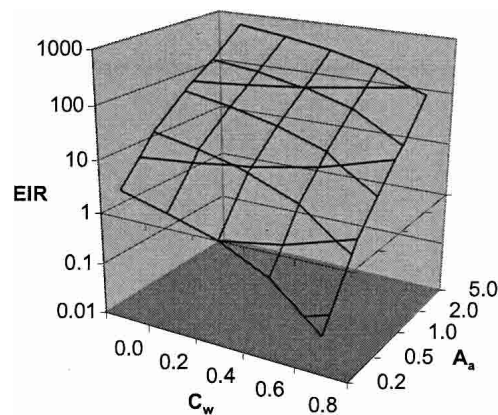

FIGURE 4. Sensitivity of baseline annual entomologic inoculation rate (EIR) to total aquatic habitat availability (A_a) over the range of 0.2–5 ovipositions per night per aquatic habitat-seeking vector, and proportional coverage with a water management intervention (C_w).

gaps in our knowledge of other crucial aspects of malaria vector ecology. Very little is know about larval bionomics or adult mating, sugar feeding, and oviposition behaviors of wild Afro-tropical anophelines, despite the key role that these factors may play in vector ecology and the propagation of *Plasmodium* refractory traits in otherwise susceptible wild populations.[44,45] Improved sampling tools and analytical models are urgently needed to measure these poorly understood processes directly in the field.

Resource availability models combined with new sampling methods for females seeking other important resources, notably aquatic habitats, could facilitate quantification of their variation across space and time and direct elucidation of their influence upon malaria transmission. The spatial ecology of malaria depends not only on distance and landscape structure, but also on the dispersal range and mortality rate of mosquitoes, which in turn depend upon the length of time spent foraging for resources.[40,42] Quantification of local resources using availability-based biodemographic models[70] could therefore facilitate rational evaluation of connectivity between sampling points in landscape ecology models of mosquito population dynamics, dispersal, gene flow, and pathogen transmission. Such integrated models will be essential for realistic pre-implementation evaluation of both traditional vector control methods[42] and possible alternatives such as malaria-refractory transgenic mosquitoes.[44,45]

While such theoretical advances are clearly important, practical realization of integrated malaria control must be prioritized. The integrated control package simulated here bears a particular resemblance to successful programs in Zambia where extensive water management, larviciding, housing improvement, bed net use, and cattle rearing were complemented by clinical management of human infections.[8,21,24] Industrial investment of the magnitude that supported malaria control in the Zambian copper belt[8,21,24] remains exceptional, but increased public funding through initiatives such as the Global Fund for HIV, Tuberculosis and Malaria[71] may make the strategies evaluated here seem less far-fetched in the near future. Successful environmental management of malaria in the Zambian copperbelt is rapidly receding from living memory and the skills to implement similar programs are thinner on the ground than ever before. As the broader field of environmental science moves forward at increasing pace, malaria research and control needs to reintegrate these disciplines and catch up on lost time. Environmental management requires integration of diverse and specialized skills, which are currently lacking in sub-Saharan Africa where they are needed most. Such essential capacity in relevant environmental disciplines can be fostered through the basic and applied ecologic research that will be needed to fill the knowledge gaps left by the post-DDT era.[22,72] Infrastructure and human capacity building in clinical, public health, and environmental disciplines should be prioritized so that growing financial support for tackling malaria can be translated into truly integrated control programs.

Authors' addresses: Gerry F. Killeen, Ifakara Health Research and Development Centre, PO Box 53, Ifakara, Kilombero District, Tanzania and Department of Public Health and Epidemiology, Swiss Tropical Institute, Basel, CH-4002, Switzerland, Telephone: 255-748-477-118, Fax: 255-23-262-5312, E-mail: gkilleen@ifakara.mimcom.net. Aklilu Seyoum, Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia. Bart G. J. Knols, Entomology Unit, Food and Agriculture Organization/International Atomic Energy Agency, Agriculture and Biotechnology Laboratory, A-2444 Seibersdorf, Austria.

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